72. (Once amended) The method of claim 70, wherein the disease state is cancer.

73. (Once amended) The method of claim 70, wherein the disease state is restenosis.

74. (Once amended) The method of claim 68, wherein the cell cycle kinase is IκB-α.

75. (Once amended) The method of claim 74, wherein the disease state is inflammation

76. (Once amended) A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 48.

REMARKS

Claims 48-76 are pending in the application. The application claims have been amended to revise the claim dependency and to clarify what it is that the Applicants regard as the invention. The application abstract has also been amended to identify the generic structure of the claimed compositions. The specification has also been amended to clarify the application parentage. No new matter has been added to the application by way of these amendments. A marked-up version of the amended claims is attached as Appendix A to this Reply.

The Examiner's specification and claim objections and rejections are each discussed and overcome as set forth below.

I. THE TRAVERSE OF ALL REJECTIONS UNDER 35 USC § 102

A. Rejection Of Claims 48-49 and 68-72 over Regnier

The Examiner has rejected claims 48-49 and 68-72 as being anticipated by Regnier. Applicants respectfully traverse the rejection.

A rejection under 35 U.S.C. 102(b) is only appropriate when every element in the rejected claim exists in a single prior art reference. None of the compounds disclosed and claimed by Regnier are within the scope of the claims of the present application. The compounds disclosed and claimed by Regnier require a tricyclic heterocycle to be linked to the pyrimidine ring of the purine. None of Applicants' compounds require such a configuration.

The Examiner specifically alleges that the compounds of Regnier (examples 2 and 27) correspond to claim 3 where R'_1 is NR_4R_5 and R_5 is an optionally substituted lower alkyl. Claim 3 was cancelled in a previous response, and Claims 48-76 are the subject of the present examination. Applicants assume that the Examiner intends to point to Claim 56, and request clarification if this assumption is mistaken. In any event, the rejection is incorrect, in that the compounds of Regnier, as disclosed in examples 2 and 27, still require that the pyrimidine ring be substituted to a tricyclic heterocycle, and cannot possibly fall within the scope of the present claims.

Applicants respectfully submit that the rejection of claims 48-49 and 68-72 as being anticipated by Regnier is incorrect, and should be withdrawn.

B. Rejection Of Claims 48-53, 56-57, 61, 64 and 68-76 over WO 97/20842

The Examiner has rejected claims 48-53, 56-57, 61, 64 and 68-76 under 35 USC §102(a) as being anticipated by WO 97/20842. Applicants respectfully traverse the rejection.

Applicants do not agree with the Examiner's rejection, because, apart from any other consideration, terms such as alkyl, "alcoylene", "aryle", etc., are not defined in the WO 97/20842. specification, and one of ordinary skill has no way of determining the scope of the claimed compounds. Additionally, there is no method taught for preparing the claimed compounds. Nonetheless, to expedite prosecution of the present application, Applicants have amended the claims (with a proviso that when R_1 is benzyl, X is -NH-, and R_3 is NR_4R_5, in which R_4 is hydrogen and R_5 is lower alkyl of C_{1-4} substituted by hydroxy or amino, R_2 is not lower alkyl of C_{1-4}), in order to avoid any possibility that the claims of the instant application have the potential to interfere with the claims of WO 97/20842. Applicants reserve the right to pursue the canceled material in a continuing application.

Applicants respectfully submit that the rejection of claims 48-53, 56-57, 61, 64 and 68-76 under 35 USC §102(a) as being anticipated by WO 97/20842 is now moot.

C. Rejection Of Claims 48-53, 56-57, 61, 64 and 68-76 over WO 97/16452

The Examiner has rejected claims 48-53, 56-57, 61, 64 and 68-76 under 35 U.S.C.§ 102(a) as being anticipated by WO 97/16452. Applicants respectfully traverse the rejection.

WO 97/16452 is not prior art to the claimed invention. The '452 reference was published as an International Publication date on May 9, 1997 which is after the filing date of any subject matter encompassed by the instant application.

Applicants submit that the rejection of claims 48-53, 56-57, 61, 64 and 68-76 under 35 U.S.C.§ 102(a) as being anticipated by WO 97/16452 should be withdrawn.

D. Rejection Of Claims 48-53, 56-57, 61, 64 and 68-76 over Norman

The Examiner has rejected claims 48-54, 56-57, 61, 64 and 68-76 as being anticipated by Norman under 35 U.S.C. 102(b). Applicants respectfully traverse the rejection.

The Norman reference does not anticipate the claims of this invention, since the proviso of claim 48 specifically excludes olomoucine as disclosed in Norman. Additionally, Norman cannot be prior art under 35 U.S.C. 102(b), as the Norman reference was not published more than one year before the priority date for the instant application.

Applicants submit that the rejection of claims 48-53, 56-57, 61, 64 and 68-76 under 35 U.S.C.§ 102(b) as being anticipated by Norman should be withdrawn.

E. Rejection Of Claims 48-49, 51, 56, and 76 over McAfee

The Examiner has rejected claims 48-49, 51, 56, and 76 under 35 U.S.C.§ 102(b) as being anticipated by McAfee. Applicants respectfully traverse the rejection.

The McAfee reference requires endo-2-norborbornyl or cyclopentyl in the R_1 position. The proviso of Claim 1 excludes the compounds as disclosed and claimed in McAfee.

Applicants submit that the rejection of claims 48-49, 51, 56, and 76 under 35 U.S.C.§ 102(b) as being anticipated by McAfee should be withdrawn.

F. Rejection Of Claims 48-49, 51, and 56 over Seyama

The Examiner has rejected Claims 48-49, 51, and 56 under 35 U.S.C.§ 102(b) as being anticipated by Seyama. Applicants respectfully traverse the rejection.

The Examiner points to compound 35 of Seyama as being within the scope of Applicants' claims, because it "corresponds to R_3 = heteroaralkyl". However, even supposing that the Seyama substitution could be considered as a heteroaralkyl (which it cannot), heteroaralkyl is not a choice for R_3 in the instant application.

With respect to compound 39 of Seyama, this is not within the scope of Applicants' claims as amended (with the proviso that R_2 and R_3 cannot both be lower alkyl)).

Applicants submit that the rejection of claims 48-49, 51 and 56 under 35 U.S.C.§ 102(b) as being anticipated by Seyama should be withdrawn.

G. Rejection Of Claims 48-49, 51, and 56 Over De Azevedo

The Examiner has rejected claims 1-2, 8-9 and 37-46 under 35 U.S.C. § 102(a) as being anticipated by De Azevedo.

This rejection is believed to be improper because the De Azevedo reference is not prior art to the claimed invention. The support for the pending application claims was found in the application specification filed on August 2, 1996. For this reason, the Applicants respectfully request that the Examiner withdraw his rejection based upon De Azevedo.

II. TRAVERSE OF THE OBVIOUSNESS REJECTIONS

A. Rejection of Claims 48-53, 56-57, 61, and 68-76 over Vesely

The Examiner has rejected claims 48-53, 56-57, 61, 64 and 68-76 as being unpatentable for obviousness over Vesely. The Examiner alleges that, although the proviso of Claim 1 removes olomoucine, it does not remove homologues of olomoucine from claim 1.

Applicants respectfully submit that the proviso of Claim 1, providing that when R_1 is benzyl, X is -NH-, and R_3 is NR_4R_5, in which R_4 is hydrogen and, R_5 is lower alkyl of C_{1-4} substituted by hydroxy or amino, then R_2 is not lower alkyl of C_{1-4} obviates this ground of rejection. Olomoucine, or its carbon homologues, do not fall within the scope of the claims of the instant invention.

Applicants submit that the rejection of claims 48-53, 56-57, 61, 64 and 68-76 as being unpatentable for obviousness over Vesely should be withdrawn.

B. The Moschel Obviousness Rejection

The Examiner rejected claims 48 and 55 for being obvious over the Moschel reference. The Examiner notes that the compounds 4a, 4c, 4e and 4f differ from the claimed compounds only in that they lack the 9-methyl of the claims.

Moschel claims purines that are substituted at the 6-position by oxygen derivatives. Although not agreeing with this ground of rejection, Applicants have amended claim 48 to remove the definition of X as oxygen or sulfur.

Accordingly, the rejection of claims 48 and 55 as being obvious over Moschel is now moot. Applicants reserve the right to pursue claims to compounds of Formulas I in which X is oxygen or sulfur in a continuing application.

III. TRAVERSE OF THE 35 U.S.C. §112, 2¶ REJECTIONS

The Examiner rejected Claims 48-76 under 35 U.S.C. §112, Second Paragraph on several different grounds. The Examiner's claim rejections are each overcome or traversed as set forth below.

The Examiner rejected many of the application claims because he believes that the terms and/or definitions are indefinite. Applicants respectfully traverse these rejections, as follows:

1. The Examiner alleges that the term heteroalkyl is indefinite. The Examiner's attention is drawn to the specification on page 14, lines 1-5, where support for the term heteroalkyl is found as follows:

> "Heteroalkyl" refers to the group -R-Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstitued or substituted with e.g., halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino amido, carboxyl, aryl aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulamido and the like."

Accordingly, the term "heteroalkyl" is not indefinite.

2. Likewise, the Examiner alleges that the term "heterocycle" is indefinite. The Examiner's attention is drawn to the specification on page 13, lines 6-12, where support for the term heterocycle is found as follows:

> "Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (e.g., morpholoino, pyridyl or furyl) or multiple condensed rings (eg, naphthpyridyl, quinoxalyl, quinolinyl, indolizinyl, or benzo[b]thienenyl) and having at least one hetero atom, such as N, O, S, within the ring, which can optionally be unsubstitued or substituted with, e.g., halogen, lower alkyl, lower alkoxy, alkythio, acetylene, amino,

amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol , sulfamido and the like."

Accordingly, the term "heterocyclyl" is not indefinite.

3. Claim 65 has been amended to remove the term "heterocyclyl" as a definition, and thus this ground of rejection is moot.

4. The Examiner alleges that the term "cycloheteroalkyl" is indefinite. The Examiner's attention is drawn to the specification on page 14, lines 17-18, where support for the term cycloheteroalkyl is found as follows:

"cycloheteroalkyl" refers to a cycloalkyl group wherein one or more of the ring atoms is replaced with a heteroatom (e.g., N, O, S or P)."

Accordingly, the term "cycloheteroalkyl" is not indefinite.

5. The Examiner alleges that the term "acyl" is indefinite. The Examiner's attention is drawn to the specification on page 12, lines 10-11, where support for the term acyl is found as follows:

"Acyl" denotes groups -C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, ary, substituted aryl and the like as defined herein."

Accordingly, the term "acyl" is not indefinite.

6. The Examiner objected to the phrasing "disease state characterized by cell proliferation". Although not necessarily agreeing with this rejection, Applicants have amended the claims to read "disease state characterized by abnormal cell proliferation".

7. The Examiner alleges that the term "amido" is indefinite. The Examiner's attention is drawn to the specification on page 12, lines 14-19, where support for the term amido is found as follows:

> "Amido denotes the group -C(O)NRR' where R and R' may be independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein."

The point of attachment is clearly delineated, as are the definitions of R and R'. Accordingly, the term amido is not indefinite.

8. The term "graft-host disease" has been amended to accord with the Examiner's suggested "host-vs-graft disease".

9. The Examiner states "(I)n R_1', optionally substituted with what?". Applicants request clarification of the question, as it is not understood. All optional substitutions of the terms claimed for R_1' are clearly set forth in the specification, and the claims have to be read in light of such definitions.

10. The term alkylthiol has been replaced with the term "alkylthio".

11. The Examiner alleges that the potential substituents listed in claim 63 are molecules and not moieties. Applicants respectfully traverse. 4-Methoxybenzyl and 3-phenylpropyl are moieties, and one of ordinary skill would understand what is intended

by the terms "(RS)-leucinol, L-histidinol, or (R)-2-amino-3-phenyl-1-propanol". Nonetheless, Applicants have amended those terms in claim 63 to indicate that the moieties are connected to the ring via the amino group [(RS)-N-leucinylol, (L)-N-histidinylol, or (R)-N-(2-amino-3-phenyl-1-propanolyl)].

12. The Examiner's objection has been overcome by canceling the word "inhibitor" from claim 74.

13. Claims 51-76 have been amended to recite the proper dependencies.

14. The Examiner alleges that a number of the disorders of claim 71 are not cell proliferative disorders. Applicants respectfully disagree.

All of the disease states listed are either primarily cell proliferative disorders (cancer, rheumatoid arthritis, systemic lupus erythematosis, multiple sclerosis, diabetes, and graft versus host disease), or have cell proliferation as a part of the sequelae of the disease (gout, diabetes). Pathological cell proliferation may also be the result of wounding, including surgical wounding, as in the case of restenosis.

For example, cancer, is a disease in which processes regulating growth-control of the cell of a given tissue are disrupted. Cancers are most commonly treated with agents that inhibit the proliferation of cells, such as nitrogen mustards, ethylenimines and methylmelamines, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, pyrimidine analogs, and a variety of other drugs. Anti-cancer drugs inhibit the mitotic cycle of a dividing cell.

Rheumatoid arthritis, systemic lupus erthymatois, Type I diabetes and multiple sclerosis are autoimmune disorders Ann. Neurol. (1994), 36(Suppl.),S103-S107, Lupus (1998),7(9), 597, Arthritis and Rheumatisism (2001), 44(5), 1013) (Autoimmunity and Autoimmune Disease. In: Immunology. 1985. Ed. I. Roitt et al. Gower Medical Publishing. London, NY. Chapter 23 p. 23,2 see Fig. 23.6). These disorders are characterized by the undesirable replication of clones of leukocytes that attack "self-antigens". The self-antigen in multiple sclerosis is myelin. The self-antigens in type 1 diabetes are located on pancreatic cells. In rheumatoid arthritis and SLE multiple self-antigens may be present on diverse organs and tissues, such as kidney, joints and skin. In rheumatoid arthritis clones of leukocytes produce proinflammatory cytokines that also stimulate the proliferation of another population of cells, known as synoviocytes which create the classical fibrotic lesions in the joints of individuals with the disorder.

Autoimmune disorders are often treated with agents that suppress the proliferation of cells. Examples of anti-proliferative drugs are cyclosporine, adrenocortical steroids (prednisolone, prednisone), cytotoxid drugs, such as those used in cancer chemotherapy, including azathiprine, mycophenolates, and cyclophosphamide.

Graft vs host disease is a proliferative disorder (WO 96/08970) in which lymphocyte passively carried in an allograph mount a cell-mediated immune response against recipient tissue. Thus, graft-versus-host disease is an immunological disorder. Graft-versus-host disease is treated with agents that suppress the proliferation of the donor T-lymphocytes, such as cyclosporine.

Type I diabetes is associated with hyperproliferation of the smooth muscle cells in the vasculature of the eye, a condition known as diabetic retinopathy. Also, patients with

Type I diabetes most frequently succumb to kidney failure which due to over production of mesangial cells or glomerular epithelial cells (WO 95/19171). As described above, Type I diabetes is also an autoimmune disorder.

Restenosis is a proliferative disorder (Cur. Opine. Mol. Ther. (2001), 3(3) 265). It is often a sequela of trauma or surgical injuries in which the proliferation of smooth muscle cells in the intima of blood vessels is stimulated. The overgrowth of the cells may occlude the vessels leading to infarction.

Applicants respectfully submit that the disorders of claim 71 are all cell proliferative disorders, and accordingly the rejection of Claim 71 should be be withdrawn.

15. Claim 50 has been amended to change the comma into a period, as suggested by the Examiner.

16-17. Claim 48 has been amended to eliminate the semi-colon and the superfluous use of the term "or", as suggested by the Examiner.

18. The Examiner's objection to "the second choice on page 4, line 1" is assumed to be a reference to the use of 4-bromoanilino as a definition of R_1' in claim 62. Applicants request clarification if this assumption is mistaken. In any event, the word "4-bromoanilino" has been changed to "4-bromophenyl" in order to express the intent of Applicants.

19. The Examiner correctly points out that the proviso of claim 48 "R_3 is not lower alkyl" is incorrect. What was intended was that when R_3 is NR_4R_5, in which R_4 is hydrogen and R_5 is lower alkyl of C_{1-4} substituted by hydroxy or amino, R_2 is not lower alkyl of C_{1-4}. Applicants have amended claim 48 accordingly.

20. The Examiner rejected claim 68 as being indefinite because, according to the Examiner, the claim could cover all known disease states. Applicants respectfully traverse the rejection.

Claim 68 is limited to disease states alleviable by treatment with a cell cycle kinase inhibitor. This does not cover all known diseases, only those diseases attributable to .the undesirable proliferation of cells. For example, Kinase inhibitors would not be useful in treating arrhythmias, congestive heart failure, etc. Kinase inhibitors are known to be useful, however, in inhibiting the proliferation of any disease resulting from the abnormal proliferation of cells.

Applicants respectfully submit that the rejection of claim 68 as being indefinite because the claim could cover all known disease states should be withdrawn.

IV. TRAVERSE OF THE 35 U.S.C.112, ¶1 CLAIM REJECTIONS

Claims 48-76 are rejected under 35 U.S.C.112 first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner's claim rejections are overcome or traversed as set forth below:

A. The Examiner stated: "-O-" for X is clearly new. Oxo, the original language, is an oxygen atom, double bonded to a carbon." Applicants respectfully traverse the rejection.

Applicants are unaware of any definition of oxo that includes a carbonyl. The Oxford dictionary of chemistry defines oxo as "a prefix indicating the presence of oxygen in a compound". Applicants submit that the use of -O- in place of oxo is appropriate, and the rejection should be withdrawn.

B. The Examiner rejected claim 48 because "thio was replaced with mercapto." The Examiner maintains that mercapto as a substituent of R_3 is new matter. However, in the specification, on page 10, line 7, "thiol" is listed as being synonymous with "mercapto." Applicants request that this basis for a rejection of Claim 48 be withdrawn.

C and D. The Examiner rejects the choice of "substituted aralkyl" in R_1' because it lacks description in the specification. The Examiner's attention is drawn to page. 13, lines 19-23, of the specification, where "Aralkyl" is defined as "the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, alkoxy, alkylthio, acetylene, aminol amido, carboyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyanolthiol, sulfamidoand the like."

Consequently, the term "substituted aralkyl" is fully defined in the specification, and the rejection should be withdrawn.

E and F. The Examiner alleges that the proviso lacks description and that the claim has been expanded. Applicants respectfully submit that the newly added provisos do not expand the claims beyond their original scope. However, even if the scope was expanded, Applicants are entitled to claim their invention as they wish, and as long as the claims are supported in the specification, claims with provisos that differ from those of the original claims are valid.

G. The Examiner rejects the term "alkoxy" in Claim 48 as being broader than that allowed by the specification.

Applicants, while not necessarily agreeing with the Examiners rejection (or even understanding it - why is the term alkoxy not allowed by the specification?) have amended claim 48 in several locations to define the term "alkoxy" as "lower alkoxy".

Accordingly, the rejection that relates to the term "alkoxy" in Claim 48 being broader than that allowed by the specification is now moot.

H. The Examiner rejects the term "ethynyl" in Claim 48 as being broader than the acetylene of page 13, line 3, of the specification. Applicants submit that the term "ethynyl" is synonymous with the term "acetylene" - both terms indicate two carbon atoms linked by a triple bond (compare the series ethane, ethylene, ethanol, all with two carbon atoms). Ethynyl is the preferred IUPAC name, acetylene is the "trivial" name.

I. The Examiner alleges that the substituent list at page 2, line 8 is not supported for the choice of heteroarylalkyl (also for the definition of R_3). Applicants respectfully submit that the claims are part of the specification, and if Applicants wish to set forth specific substituents that are not detailed in the body of the specification, they are entitled to do so.

J. The term "pharmaceutically acceptable salt" of claim48 has been replaced by the term "acid addition salts and cationic salts". These terms are supported in the specification at page 15, lines 10-21.

K. The Examiner alleges that the utility recited in claim 68 lacks description in the specification. Applicants respectfully traverse the rejection.

The Examiner's attention is drawn to the specification on page1, lines 12-18, which recites the following:

> "This invention concerns 2,6,9 trisubstituted purines that have been discovered to be selective inhibitors of cell cycle kinases and, as such, the compounds are inhibitors of cell proliferation. The 2,6,9 trisubstituted purines are useful in for example in- treating autoimmune diseases, e.g. rheumatoid arthritis, lupus, type I diabetes, multiple sclerosi, etc., in treating cancer, cardiovascular disease, such as restenosis, host vs graft disease, gout, polysystic kidney disease and other proliferative diseases where pathogenesis involves abnormal cell proliferation."

Thus, the invention is not limited to inhibitors of CDK-2 kinases, and accordingly the rejection should be withdrawn.

L. The Examiner alleges that the term "substituted heteroalkyl" is not found in the specification. In fact, the term "heteroalkyl", which is defined on page 14, lines1-5 of the application as -R-Het, in which Het can be both substituted and unsubstituted heterocyclic groups. Accordingly, the term "substituted heteroalkyl" has been removed as a choice for R_1', as it is duplicative.

M. In point 6 (to which the Examiner refers), the Examiner objected to the phrasing "disease state characterized by cell proliferation". Although not necessarily agreeing with this rejection, Applicants have amended the claims to read "disease state characterized by abnormal cell proliferation".

Accordingly, this ground of rejection is overcome.

N. The Examiner rejects the choice of "substituted heteroarylalkyl" in R_2 and R_3 because it lacks description in the specification.

In fact, the term "heteroarylalkyl" is defined on page 14, lines 6-10, as follows:

> "Heteroarylalkyl" refers to the group -RHet-Ar where HetAr is an heteroaryl group and R is lower alkyl or substituted lower alkyl group. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxy, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyanolthiol, sulfamido and the like."

Accordingly, the term "substituted heteroarylalkyl" is fully supported in the specification, and the rejection should be withdrawn.

V. TRAVERSE OF THE 35 U.S.C. 112, 1¶ REJECTION OF CLAIM 70

The Examiner rejected claim 70 under 35 USC Section 112, first paragraph for containing subject matter not described in the specification. In the rejection, the Examiner stated:

> "A proliferative disorder is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers pre-cancer conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with arteriosclerosis, glomerular nephritis, clonal proliferative disorders including the various myelodysplastic syndromes, such as refractory anemia, certain types of abnormal wound healing, different types of abnormal angiogenesis, pulmonary fibrosis, macular degeneration, meyeloproliferative disorders such as primary polycythemia and myelofibrosis, and rheumatoid arthritis. There is no such thing that an agent which effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work."

From this excerpt of the rejection, the Examiner acknowledges that the diseases mentioned are proliferative disorders causing abnormal tissue growth. Abnormal tissue growth is due to the uncontrolled growth of cells that make up the tissues. The proliferation of cells is due to regulatory enzymes that control the cell cycle. The basic mechanisms via enzymatic control are alike in all cells. Thus, these proliferative diseases share a basic mechanistic abnormality that culminates in hyperproliferation. As described in the specification, the invention consists of compounds that inhibit CDK-2 and IkB-a. These two enzymes regulate the cell cycle in a wide variety of cells. Inhibition of these enzymes will modulate the replication of all the cells described.

For example, rheumatoid arthritis (RA) is an inflammatory disease cause by the excessive proliferation of cells that secrete pro-inflammatory cytokines. Inhibition of the proliferation of these cells decreases the number of cells producing these cytokines. Inhibition of the proliferation of proinflammatory leukocytes is the basis for a variety of treatments for RA. A treatment for RA is cyclophosphamide, a cytotoxic drug which is also used to treat cancer (Chemotherapy of Neoplastic Diseases, 1995. In: Gilbert and Goodman's The Pharmacological Basis of Therapeutics, Chapter 51, p. 1239. McGraw-Hill).

Systemic lupus erthematosis (lupus) is a connective tissue disorder. One of the manifestations of the disease is hyperproliferation of fibroblasts leading to excess collagen deposition (fibrosis) in many tissues. Treatments for lupus include methotrexate, another anti-neoplastic drug, which is cytotoxic to cells. Methotrexate is used to proliferative disorders, including lupus and psoriasis, in addition to cancer Chemotherapy of Neoplastic Diseases, 1995. In: Gilbert and Goodman's The Pharmacological Basis of Therapeutics, Chapter 51, p. 1246. McGraw-Hill.

Multiple sclerosis is an autoimmune disorder characterized by the proliferation of auto-reactive T cells that attack myelin. One of the methods of treating MS are agents that inhibit the proliferation of the T-cell clones with immunosuppressives. In addition to methotrexate and cyclophosphamide chlorambucil, vincristine, vinblastine and dactinomycin are used to treat both cancer and immunoproliferative disorders (Drugs used for Immunodulation, 1995. In:Gilbert and Goodman's The Pharmacological Basis of Therapeutics, Chapter 52, p. 1239. McGraw-Hill Cancer, which can occur in most tissues, is due to a breakdown in the normal regulatory pathways of the cell cycle. Most

cancer chemotherapies are almost all non-selective inhibitors of growth of any dividing cell. Thus, cisplatin, ardriamycin, alkylating agents, antimetabolites, and antagonists have all been used to treat many different types of cancer. The non-selective nature of these agents, that is there inhibition of growth of normal cells, leads to unpleasant and serious side effects of the drugs. This has driven the desire to find targets unique to cancer cells.

Accordingly, the rejection of claim 70 under the first paragraph of section 112 should be withdrawn.

VI. TRAVERSE OF THE 35 USC 112, 1¶ REJECTION OF CLAIM 72

Rejection of Cancer Treatment Claims

The Examiner rejected claim 72 under 35 U.S.C. 112, first paragraph, because:

> The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure how to get a compound to be effective against cancer generally, or even a majority of cancers."

Applicants respectfully traverse this rejection.

Neoplasia, which can occur in most tissues, is due to a breakdown in the normal regulatory pathways of the cell cycle. Most cancer chemotherapies have utilized this general principle to devise treatments for tumors. They are almost all non-selective inhibitors of growth of any dividing cell. Thus, cisplatin, ardriamycin, alkylating agents, antimetabolites, and antagonists have all been used to treat many different types of cancer. The non-selective nature of these agents, that is there inhibition of growth of

normal cells, leads to unpleasant and serious side effects of the drugs. This has driven the desire to find targets unique to cancer cells, such as CDK-2 inhibitors.

The rejection of claim 72 under 35 U.S.C. 112, first paragraph, should be withdrawn.

VII. TRAVERSE OF THE 35 U.S.C. § 112, 1¶ REJECTION OF CLAIM 75

The Examiner rejected claim 75 under the first paragraph of section 112 for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make or use the invention.

The Examiner stated:

> "Enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, caused for the problem and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammation arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally."

Applicant's respectfully traverse the rejection. Inflammation is described in Goodman and Gilman's The Pharmacological Basis of Therapeutics (1996. Eds. Hardman, Limbirda, Molinoff, Ruddon, and Gilman McGrawHill. NY. p618-619) as follows:

> "The inflammatory process involves a series of events that can be elicited by numerous stimuli (*e.g.*, infections agents, ischemia, antigen-antibody

> interactions, and thermal or physical injury). Each type of stimulus provokes a characteristic pattern of response that represents a relatively minor variation on a theme. At a macroscopic level, the response usually is accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia), and pain. Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms: (1) an acute transient phase, characterized by local vasodilatation and increased capillary permeability; (2) a delayed subacute phase, most prominently characterized by infiltration of leukocytes and phagocytic cells; and (3) a chronic proliferative phase, in which tissue degeneration and fibrosis occur. Many different mechanisms are involved in the inflammatory process (Gallin *et al.*, 1992; Kelly *et al.*, 1993). The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury, although in some situations and diseases the inflammatory response may be exaggerated and sustained for no apparent beneficial reason.

Thus, although etiologic factors and tissues vary, an inflammatory response is basically the same regardless of the tissue. Inflammation is the culmination of a series of biological events and whatever the initiating event the steps are the same. Drugs have been developed to inhibit various steps of the inflammatory response and these drugs have been used in many different types of inflammatory disorders. Thus, steroids have been used in pulmonary inflammation caused by asthma, in rheumatoid arthritis, multiple sclerosis, glomerulonephritis, cyclosporin is used to inhibit the growth of T-cells in many inflammatory disorders including Behcet's syndrome, uveitis, atopic dermatitis, psorasis, rheumatoid arthritis, Crohn's disease and biliary cirrhosis.

Accordingly, the rejection of claim 75 under the first paragraph of section 112 should be withdrawn.

VIII. TRAVERSE OF THE SECTION 112, 1¶ REJECTION OF CLAIMS 68-74

The Examiner rejected claims 68-74 under 35 U.S.C.§ 112 first paragraph on several grounds, each of which is discussed and traversed below.

I. The Examiner's rejection is based upon the premises that:

> The compounds are disclosed to be CDK2 inhibitors. There is no reason to think that one of ordinary skill in the art could, without undue experimentation, treat such difficult disorders with such compounds.

The Examiner is wrong in his conclusion. It is well known in the art that CDK2 inhibitors are useful for the treatment of the disclosed disease states. The compounds of the invention are CDK2 inhibitors as shown by two Example assays which directly measured the activity of the enzyme and in *in vitro* tests that show the effect of the compound on the proliferation of cells. Both assays are accepted in the art as verification of the activity of growth inhibitory compounds.

Accordingly, there is no "undue experimentation" required by one of ordinary skill, and the Examiner's rejection should be withdrawn.

II. The Examiner goes on to say:

> "Although olomoucine itself is not potent enough to be effective, the testing presented in Table 6 established that these compounds are either less effective as CK2 inhibitors than olomoucine, or are not effective to actually inhibit cell proliferation even in this crude test".

The Examiner appears to doubt the asserted utility of the claimed invention has the burden of proof to provide reasons for this disbelief. "(T)he Examiner's unsupported skepticism as to the utility of the claimed invention does not provide a legally acceptable basis for rejecting the claims". Ex parte Krenzer, 199 USPQ 227, 229 (POBA 1978). "Where assertions of utility are believable on their face and straight forward, and no

reason or authority in variance has been advanced, the disclosed utility must be accepted as accurate." In re Bundy, 642 F.2d 430, 209 U.S.P.Q. 18 (CCPA 1981).

Both olomoucine and the compounds of the invention inhibit the proliferation of cells. Olomoucine inhibits the rate of cell growth by 50% with 70 ug/ml. The specification discloses that the compounds of the invention inhibit the rate cell growth by 50% between concentrations of .05 ug/ml to 100 ug/ml. Thus, the compounds of the invention decrease cell proliferative rates in an art recognized assay.

Therefore, the assertion of utility is believable. The specification on page 46-56, sets forth in detail *in vitro* and *in vivo* testing protocols for efficacy of a compound for the claimed utility. These testing protocols are described in the scientific literature and are accepted as predictive of activity. The present methods of treatment are "believable in view of contemporary knowledge in the art".

Applicants respectfully submit that the rejection of Claims 68-74 under 35 U.S.C §112, first paragraph, be withdrawn.

III. The Examiner further contends that:

> The inclusion of gout in claim 71 makes no sense at all. Patients with gout are normally told to avoid high purine foods, in order to reduce uric acid secretion.

Patients with gout often have an inflammatory lesion resulting from the crystals of uric acid. The inflammation, like any other inflammation, may be treated with any agent that reduces the number of proliferating clones of immunocytes. Therefore, compounds

that inhibit CDK-2 and IkB-a-kinases will inhibit the growth of populations of inflammatory cells.

Applicants respectfully submit that the rejection of Claims 68-74 under 35 U.S.C §112, first paragraph, be withdrawn on these grounds.

IV. The Examiner also contends that:

> Lupus and MS in Claim 71 are intractable nervous system disorders that "no one has been able to treat these with CDK2 inhibitors.

Lupus and MS are autoimmune disorders. Lupus is a generalized connective tissue disorder (Dorland's Illustrated Medical Dictionary). In lupus the proliferation of autoreactive T cell clones stimulates the division of fibroblasts, which are connective tissue cells. The fibroblasts secrete collagen, a connective tissue protein, in abnormally high amounts. Lupus has been treated as described above with anti-neoplastic agents that inhibit cell growth. CDK2 inhibitors also inhibit cell growth.

MS is an autoimmune disorder in which clones of autoreactive T cells mount an immune response to myelin.

It should be noted that WO 00/55161 discloses biarylmethylaminopurines as potent cyclin/CDK inhibitors and antiproliferative agents. Furthermore, their use in the treatment of rheumatoid arthritis, lupus, type 1 diabetes, multiple sclerosis, cancer, restenosis, gout, and other proliferative diseased is disclosed.

Applicants respectfully submit that the rejection of Claims 68-74 under 35 U.S.C §112, first paragraph, be withdrawn on these grounds.

V. The Examiner is unclear about which compounds are IkB-a inhibitors. The methods used to determine the inhibitory effect of the compound of the invention on IkB-a are described in Examples 9, and the results are shown in Table 8 for specific compounds.

Applicants do not understand the relevance of the statement that little is known about these kinases. Applicants have shown how to make the inhibitors, and shown how such inhibitors are tested to demonstrate that they are IκB-α inhibitors, and their effects on the proliferation of cells (see Example 9).

Applicants respectfully submit that the rejection of Claims 68-74 under 35 U.S.C §112, first paragraph, be withdrawn on these grounds.

IX. THE DOUBLE PATENTING REJECTION

The Examiner rejected certain application claims under the judicially created doctrine of obviousness-type double patenting in view of claims 1-6 of U.S. Patent No. 5,866,702.

The applicants acknowledge this grounds for rejection and are prepared to file a terminal disclaimer to overcome the rejection should any application claim be allowed by the Examiner.

X. THE SPECIFICATION OBJECTIONS

The Examiner objected to the specification priority claim. The Examiner's objection has been overcome by amending the priority claim in this Reply.

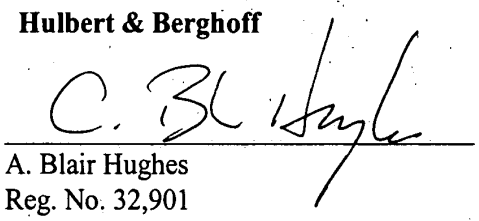
The Examiner objected to the application Abstract. This objection has been overcome by canceling the Abstract from the specification and replacing it with a new Abstract that identifies the generic composition formula.

CONCLUSION

The amendments and/or statements in favor of patentability presented above are believed to render pending application claims 48-76 allowable. Favorable reconsideration and allowance of all pending application claims is, therefore, courteously solicited.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff

Dated: April 22, 2002 By: 

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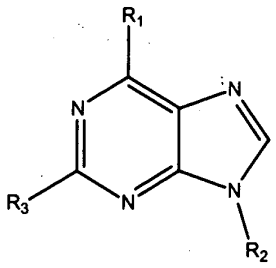
APPENDIX A

Marked Up Specification Paragraphs And Claims Pursuant To 37 CFR 1.121

IN THE CLAIMS:

48. (Once amended) A compound having the formula:



wherein:

R_1 is -X-R_1'; in which R_1' is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, hetaryl, substituted hetaryl, and heteroalkyl,[and substituted heteroalkyl] and X is -NH-,[-O-, -S-,] or -SO_2;

R_2 is lower alkyl optionally substituted with one, two or three groups selected from hydroxy, lower alkoxy, halogen, mercapto, alkylthiol, amino, amido, carboxy, cyano, aryloxy, alkenyl, alkynyl, or acyl; [or]

aryl, heteroaryl, arylalkyl or heteroarylalkyl where the ring portion of each is optionally substituted with one, two or three groups selected from lower alkyl, alkoxy, halogen, mercapto, alkylthio[l], ethynyl, amino, amido, carboxy, hydroxy, aryl, aryloxy, heteroaryl, nitro, or cyano; [or]

cycloalkyl optionally substituted with one, two or three groups selected from lower alkyl, alkoxy, halogen, thiol, ethynyl, alkylthio[l], aryl, aryloxy, heteroaryl, nitro, or cyano; or

heterocyclyl; and

R_3 is halogen, hydroxy, mercapto, alkoxy, alkylthiol, lower alkyl, or $-NR_4R_5$; in which R_4 and R_5 independently are hydrogen or lower alkyl optionally substituted with one, two or three groups selected from hydroxy, alkoxy, halogen, amino, mercapto, alkylthiol, amido, carboxyl, cyano, aryloxy, or acyl; or;

aryl, arylalkyl, heteroaryl, heteroarylalkyl, or cycloalkyl where the ring portion of each is optionally substituted with one, two or three groups selected from lower alkyl, lower alkoxy, halogen, mercapto, alkylthiol, [ethynyl]acetylene, amino, amido, carboxyl, hydroxy, aryl, aryloxy, heteroaryl, nitro, or cyano;

[with the proviso that when $[R_1]R_1'$ is benzyl, X is -NH-, and R_2 is lower alkyl of C_{1-4}, R_3 is not lower alkyl of C_{2-4} substituted by hydroxy or amino]; with the proviso that when R_1 is benzyl, X is -NH-, and R_3 is NR_4R_5, in which R_4 is hydrogen and R_5 is lower alkyl of C_{1-4} substituted by hydroxy or amino, R_2 is not lower alkyl of C_{1-4}, and with the proviso that R_1 cannot be cycloalkyl or endo-2-norbornyl when R_3 is halogen, hydroxy, or alkoxy; and with the proviso that R_2 and R_3 cannot both be lower alkyl; or [a pharmaceutically acceptable salt] acid addition salts and cationic salts thereof.

50. (Once amended) The compound of claim 49, wherein R_1' is aryl, substituted aryl, aralkyl, substituted aralkyl, hetaryl, or substituted hetaryl[,].

51. (Once amended) The compound of claim [3]50, wherein R_2 is lower alkyl optionally substituted with one, two or three groups selected from hydroxy, alkoxy, halogen, amino, or acyl, or cycloalkyl optionally substituted with lower alkyl or alkoxy.

52. (Once amended) The compound of claim [4]51, wherein R_3 is $-NR_4R_5$, in which R_4 and R_5 independently are hydrogen or lower alkyl optionally substituted with one, two or three groups selected from hydroxy, alkoxy, halogen, amino, or acyl.

53. (Once amended) The compound of claim [5]52, wherein R_4 and R_5 independently are lower alkyl substituted with hydroxy or amino.

54. (Once amended) The compound of claim [6]53, wherein R_4 and R_5 are both lower alkyl substituted with amino.

55. (Once amended) The compound of claim [7]54, wherein R_4 and R_5 are both 2-aminoethyl.

56. (Once amended) The compound of claim [8]55, wherein R_2 is lower alkyl.

57. (Once amended) The compound of claim [9]56, wherein R_2 is isopropyl.

58. (Once amended) The compound of claim [10]57, wherein R_1' is 4-methoxybenzyl, pyridin-3-ylmethyl, or cyclopropylmethyl.

59. (Once amended) The compound of claim [8]55, wherein R_4 and R_5 are both lower alkyl substituted with hydroxy.

60. (Once amended) The compound of claim [12]59, wherein R_4 and R_5 are both 2-hydroxyethyl.

61. (Once amended) The compound of claim [13]60, wherein R_2 is isopropyl.

62. (Once amended) The compound of claim [14]61, wherein R_1' is 4-phenylbenzyl, 4-bromobenzyl, [4-bromoanilino] 4-bromophenyl, quinolin-3-yl, quinolin-5-yl, quinolin-6-yl, or quinolin-8-yl.

63. (Once amended) The compound of claim [4]51, wherein R_1' is 4-methoxybenzyl or 3-phenylpropyl and R_3 is (RS)-N-leucinylol, (L)-N-histidinylol, or (R)-N-(2-amino-3-phenyl-1-propanolyl).

64. (Once amended) The compound of claim [16]63, wherein R_2 is isopropyl.

65. (Once amended) The compound of claim [2]49, wherein R_1' is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, [heterocyclyl, or substituted heterocyclyl,] R_2 is lower alkyl, and R_3 is $-NR_4R_5$, in which R_4 and R_5 independently are lower alkyl substituted with hydroxy or amino.

66. (Once amended) The compound of claim [18]65, wherein R_1' is lower alkyl of 1-8 carbon atoms and R_2 is isopropyl.

67. (Once amended) The compound of claim [18]65, wherein R_1' is cycloalkyl of 3-7 carbon atoms and R_2 is isopropyl.

68. (Once amended) A method of treating a disease state in a mammal that is alleviable by treatment with a cell cycle kinase inhibitor, comprising administering to a mammal in need thereof a therapeutically effective dose of a compound of claim [1]48.

69. (Once amended) The method of claim [21]68, wherein the cell cycle kinase [inhibitor] is CDK2.

70. (Once amended) The method of claim [22]69, wherein the disease state is characterized by abnormal cell proliferation.

71. (Once amended) The method of claim [23]70, wherein the disease state is rheumatoid arthritis, lupus, diabetes, multiple sclerosis, cancer, restenosis, [graft-host disease] host-vs-graft disease, or gout.

72. (Once amended) The method of claim [23]70, wherein the disease state is cancer.

73. (Once amended) The method of claim [23]70, wherein the disease state is restenosis.

74. (Once amended) The method of claim [21]68, wherein the cell cycle kinase [inhibitor] is IκB-α.

75. (Once amended) The method of claim [27]74, wherein the disease state is inflammation

76. (Once amended) A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim [1]48.